UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte PHILIP G. ASHTON-RICKARDT and JOSEPH T. OPFERMAN

Appeal No. 2005-2616
Application No. 09/993,363

ON BRIEF

Before SCHEINER, MILLS and GRIMES, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to methods of enhancing or inducing immunity to a viral infection using cytotoxic T-lymphocytes expressing a serpin or a serpin mimetic. The examiner rejected claims 26-35, 37-40, 42-44, 48-50 and 61-74, the only claims remaining in the application, as lacking enablement. In addition, the examiner rejected claims 26-35, 37, 42-44, 48-50, 61-65, 67 and 71-73 as lacking adequate written descriptive support. We have jurisdiction under 35 U.S.C. § 134. We reverse the enablement rejection, vacate the written description rejection, and enter a new ground of rejection against claims 34 and 64.

Background

One mechanism of killing virus-infected cells involves exocytosis of lymphocytic granules from activated cytotoxic T-lymphocytes (CTLs). Perforins and lymphocyte serine proteases, termed granzymes, are released from the lymphocytic granules, and together initiate a cascade of events that results in lysis and apoptosis (programmed cell death) of the virus-infected target cells. Specification, pages 3, 14 and 15.

CTLs are also susceptible to granzymes, but activated CTLs are largely spared from autolysis during the lytic process (termed the effector phase), and continue to lyse new target cells, "suggesting a mechanism by which a CTL may protect itself from self-injury" (id., page 3). After the effector phase, most of the activated CTLs "undergo activation induced cell death (AICD)" (id.), but "some CTLs escape AICD and give rise to memory cells" (id., page 4) "that persist for many years and facilitate accelerated responses upon re-exposure to antigen[s] such as viral antigens" (id., page 3). "[T]he perforin/granzyme pathway [ ] plays a role in memory cell development" (id., page 4). Finally, high zone tolerance, "thought to be due to excessive [viral burden and] stimulation by antigen, [ ] induces the clonal exhaustion of CTLs and attenuates the development of anti-viral memory" (id., page 5). "The end result is chronic viral persistence and . . . generalized immunosuppression of T-cell responses" (id.).

"Serpins are a group of naturally occurring proteins that inhibit serine proteases" (id., page 15), and include many that inhibit granzymes. According to Bird,[1] cited on page 4 of the specification, "[o]ne of the key regions in [a] serpin is the carboxy-terminal

[1] P.I. Bird, "Regulation of Pro-Apoptotic Leukocyte Granule Serine Proteinases by Intracellular Serpins," Immunology and Cell Biology, Vol. 77, pp. 47-57 (1999)

inhibitory domain . . . [which] contains a sequence that varies from serpin to serpin and resembles the natural substrate of the target proteinase" (Bird, page 50). When a protease binds a serpin, it attempts to cleave the serpin as if it were a natural substrate, but the "hydrolysis . . . does not proceed efficiently, and the proteinase and serpin become trapped in a complex that resembles an . . . intermediate of the proteinase-substrate reaction" (id.). "The interaction between a serpin and its target proteinase typically leads to the formation of an essentially irreversible 1:1 complex, a property that gives rise to the description of serpins as 'suicide substrates'" (id.).

The specification includes a number of examples demonstrating the granzyme B inhibitory effects of a murine serpin, SPI6 (a homolog of the human ova-serpin, PI9). For example, Examples 4 and 6 demonstrate that SPI6 protects CTLs from autolysis induced by misdirected granzyme B during lysis of target cells, and also improves the potency of the CTLs (Specification, pages 74-78). Example 12 demonstrates that LCMV-infected mice transgenic for SPI6 cleared virus more rapidly and effectively than non-transgenic mice. The transgenic mice also developed higher numbers of persistent LCMV-specific memory cells, "indicat[ing] a possible role for SPI6 in protecting memory cell precursors from AICD due to granzyme B" (id., pages 85-86).[2]

The present invention is directed to "enhanc[ing] [ ] immunity by increasing the number of cytotoxic T-lymphocyte memory cells; and/or augmenting cytotoxic T-lymphocyte function; and/or augmenting cytotoxic T-lymphocyte memory cell development" (id., page 8), by expressing a serpin or serpin mimetic in cytotoxic

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[2] LCMV = lymphocytic choriomeningitis virus

T-lymphocytes. "[S]ome examples of serpin[s] useful in the . . . present invention are SPI6, PI9, PI-6, monocyte neutrophil elastase inhibitor (MNEI), PI-8, and plasminogen activator inhibitor 2 (PAI-2)" (id., page 6). PI9 in particular "has been identified in T-cells . . . [and] is a potent inhibitor of granzyme B and protects cells in vitro from perforin/granzyme killing" (id., page 4).

The Claims

Claims 26, 30, 34, 38, 42 and 64 are representative:

26. A method for enhancing or inducing immunity to a viral infection comprising expressing a serpin or a serpin mimetic in a cytotoxic T-lymphocyte of a subject by introducing an expression construct comprising a DNA segment encoding the serpin or serpin mimetic under the control of a promoter active in the cytotoxic T-lymphocyte.

30. A method for enhancing or inducing immunity to a virus comprising:
a) obtaining a cytotoxic T-lymphocyte that comprises an expression vector that comprises a DNA segment encoding a serpin or a serpin mimetic under the control of a promoter active in the cytotoxic T-lymphocyte; and
b) administering the cytotoxic T-lymphocyte to a subject in need thereof.

34. The method of claim 30, wherein the serpin or serpin mimetic inhibits granzyme activity, inhibits granzyme transcription, inhibits granzyme translation, increases granzyme degradation, or destabilizes granzyme.

38. The method of claim 30, wherein the serpin is SPI6, PI9, PI-6, monocyte neutrophil elastase inhibitor (MNEI), PI-8, plasminogen activator inhibitor 2 (PAI-2).

42. The method of claim 30, wherein the virus is HIV, LCMV, HCV, HTLV-1, HTLV-2, EBV, HBV, human cytomega[l]ovirus, Herpes simplex 1, Herpes simplex 2, hepatitis G, enterovirus, dengue fever virus, or rabies virus.

64. The method of claim 26, wherein the serpin or serpin mimetic inhibits granzyme activity, inhibits granzyme transcription, inhibits granzyme translation, increases granzyme degradation, or destabilizes granzyme.

Thus, in their broadest aspect the claims are directed to enhancing or inducing immunity to a viral infection in a subject by expressing a serpin or serpin mimetic in the subject's CTLs, or administering serpin- or serpin mimetic-expressing CTLs to a subject.

According to the specification, "[t]he terms 'enhancement' and 'enhancing' mean the increasing of immunity over a level of immunity that is already present in a subject for a short time, long time, or indefinite time. The terms 'inducement' and 'inducing' mean causing immunity in a subject where immunity is lacking, or at a substantially unmeasurably low level." Specification, page 5.

We note that appellants elected P19 and HIV in response to the examiner's requirement for an election of a single serpin and a single virus for initial examination on the merits (Restriction/Election Requirement, November 12, 2002; Supplemental Response to Restriction/Election Requirement, January 14, 2003). Nevertheless, most of the examiner's arguments in the enablement and written description rejections are directed to serpins and viruses in general, so we will assume, for purposes of this appeal, that the broader aspects of the claimed invention have been examined.

Discussion

Enablement

The examiner rejected all of the pending claims under 35 U.S.C. § 112, first paragraph, for lack of enablement (Examiner's Answer, page 5). The examiner's position is essentially that "gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect" (Examiner's Answer, page 10), and that "therapy of a viral infection with CTLs is unpredictable" (id., page 5), yet "the specification does not provide any guidance as to how to address the issues of unpredictability in the art" (id., pages 5-6). The examiner acknowledged the in vivo examples in the specification, but argued that the "SPI6 expressing transgenic mouse . . . is not a natural animal model because there

is no issue of gene delivery to cells since the mouse has the transgene in all of its cells" (id., page 8).

The examiner concluded that "it would have required undue experimentation of one skilled in the art to use the claimed invention as broadly claimed" "in view of the quantity of experimentation necessary to determine the parameters for achieving treatment of any viral function and by any route of administration as broadly claimed, the lack of direction or guidance provided by the specification [as] well as the absence of working examples with regard to a therapeutic effect" (Examiner's Answer, page 10).

The examiner bears the initial burden of showing that a claimed invention is nonenabled. "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

"[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation' . . . That some experimentation may

be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." In re Brana, 51 F.3d 1560, 1568, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). (While the Brana court referred to "usefulness", the rejection on appeal was for nonenablement. See id. at 1564, 34 USPQ2d at 1439).

We think it is fair to say that the evidence cited by the examiner establishes that both gene therapy and CTL therapy were considered to be unpredictable by those skilled in the art. But the same evidence relied on by the examiner as evidence of unpredictability also establishes that the level of unpredictability, and the amount of experimentation required in these fields, was considered to be acceptable, rather than undue, at the time of the invention. For example, both Romano[3] and Clay[4] provide evidence that hundreds of gene therapy clinical protocols have been approved worldwide for diseases ranging from HIV to cancer, despite the recognition that many biological and technical hurdles will have to be overcome before gene therapy will be clinically effective.

That being said, the invention that must be enabled to satisfy § 112 is the invention defined by the claims. See CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) ("Title 35 does not require that a patent

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[3] Romano et al., "Latest Developments in Gene Transfer Technology: Achievements, Perspectives, and Controversies over Therapeutic Applications," Stem Cells, Vol. 18, pp. 19-39 (2000)

[4] Clay et al., "Potential Use of T Cell Receptor Genes to Modify Hematopoietic Stem Cells for the Gene Therapy of Cancer," Pathology Oncology Research, Vol. 5, No. 1, pp. 3-15 (1999)

disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect."). When the claims are not limited to a method that achieves therapeutic or clinical efficacy, such efficacy is not required for the claims to be enabled.

Here, the claims are directed to enhancing or inducing immunity to a viral infection in a subject by expressing a serpin or serpin mimetic in the subject's CTLs, or administering serpin- or serpin mimetic-expressing CTLs to a subject. As discussed above, enhancing or inducing immunity merely means "increasing [ ] immunity over a level of immunity that is already present in a subject for a short time, long time, or indefinite time . . . [or] causing immunity in a subject where immunity is lacking, or . . . substantially unmeasurabl[e]" (Specification, page 5).

Thus, while the claims encompass a method that produces a therapeutically effective response, they do not require it. Cf. In re Cortright, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999) (claims to a method of "treating scalp baldness" could be enabled even if the method did not produce a full head of hair). Nor do the claims require "achieving treatment of any viral function [ ] by any route of administration" (Examiner's Answer, page 10).

We conclude that the evidence of record establishes that the claimed invention had reached "the stage at which an invention in this field becomes useful" (Brana, 51 F.3d at 1568, 34 USPQ2d at 1442) at the time of filing, despite the level of unpredictability recognized in the art. While the potential problems identified by the examiner may indeed complicate the process of effectively treating a viral infection, they need not be overcome in order to "enhance or induce" the immune response to the

infection, all that is required by the claimed methods. Thus, the examiner has not adequately explained why practicing the claimed method would have required undue experimentation.

The rejection of claims 26-35, 37-40, 42-44, 48-50 and 61-64 as lacking enablement under 35 U.S.C. § 112, first paragraph, is reversed.

Written Description

The examiner also rejected claims 26-35, 37, 42-44, 48-50, 61-65, 67 and 71-73 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention" (Examiner's Answer, page 3). Nevertheless, having reviewed the prosecution history of this case, we believe that the rejection of record is inappropriate, while the real written description issue may have been overlooked.

According to the examiner, all of the serpins listed in the specification "inhibit the enzyme activity of serine protease[s] and none . . . inhibit[s] transcription, translation or increase[s] degradation" of serine proteases (id., page 4). Thus, the examiner argued that "the specification does not provide sufficient written descript[ive] support for . . . [a] genus of serpin[s] or serpin mimetic[s]" (id., page 3) that includes members that "inhibit the transcription, translation, or increase degradation [of serine proteases] as recited, for example, in claims 34 and 64" (id., page 4).

In reviewing the prosecution history of the application, however, we believe that the issue is not, as the examiner characterized it, whether "a representative number of species [of the serpin genus] have been described" (id.). Rather, the issue is whether

there was adequate written descriptive support in the specification as filed for the June 19, 2003 amendment of claim 34 and entry of claim 64. In other words, was new matter introduced into claims 34 and 64 by the June 19, 2003 amendment?

We therefore vacate the examiner's rejection of claims 26-35, 37, 42-44, 48-50, 61-65, 67 and 71-73 under 35 U.S.C. § 112, first paragraph, and enter a new rejection against claims 34 and 64 under the same section of the statute, but for a different reason.

New Ground of Rejection

Under the provisions of 37 CFR § 41.50(b), we enter the following new ground of rejection: claims 34 and 64 are rejected under 35 U.S.C. § 112, first paragraph. This is a new matter rejection.

To satisfy the written description requirement, the specification must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [applicant] was in possession [of] . . . whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1564, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An issue arising under the written description requirement of 35 U.S.C. § 112, first paragraph, is a question of fact. Id. at 1563, 19 USPQ2d at 1116.

We note that the original version of independent claim 30, from which claim 34 depends, read as follows (emphasis ours):

> 30. A method of enhancing or inducing immunity comprising:
> a) obtaining a cytotoxic T-lymphocyte that comprises an expression vector that comprises a DNA segment encoding a **granzyme inhibitor** under the control of a promoter active in the cytotoxic T-lymphocyte; and
> b) administering the cytotoxic T-lymphocyte to a subject in need thereof.

Similarly, the original version of claim 34 read:

> 34. The method of claim 30, wherein the **granzyme inhibitor** inhibits granzyme activity, inhibits granzyme transcription, inhibits granzyme translation, increases granzyme degradation, or destabilizes granzyme.

Thus, claim 34 indicates that the genus of "granzyme inhibitors" includes members that inhibit granzyme transcription, inhibit granzyme translation, etc. This is consistent with the specification, which teaches that a "granzyme inhibitor may inhibit granzyme activity, inhibit granzyme transcription, inhibit granzyme translation, increase granzyme degradation, destabilize granzyme or inhibit granzyme function" (Specification, page 53). A granzyme inhibitor "may be one which exerts its inhibitory or activating effect upstream, downstream or directly on granzyme B including the activity and levels of granzyme B" (id., page 56). While the focus of the specification is on serpins, which are "endogenous serine protease inhibitors" (id., page 6), the specification also teaches that a granzyme inhibitor "may be a protein or fragment thereof, a small molecule, or even a nucleic acid molecule" (id., page 54). "Other suitable inhibitors include ribozymes, and antibodies (including single chain antibodies)" (id., page 56).

The amendment of June 19, 2003 narrowed the claim to read:

> 30. A method of enhancing or inducing immunity comprising:
> a) obtaining a cytotoxic T-lymphocyte that comprises an expression vector that comprises a DNA segment encoding a **serpin or serpin mimetic** under the control of a promoter active in the cytotoxic T-lymphocyte; and
> b) administering the cytotoxic T-lymphocyte to a subject in need thereof.

Dependent claim 34 was amended at the same time, in the same manner, to read:

> 34. The method of claim 30, wherein the **serpin or serpin mimetic** inhibits granzyme activity, inhibits granzyme transcription, inhibits granzyme translation, increases granzyme degradation, or destabilizes granzyme.

Nevertheless, serpins represent a sub-genus of granzyme inhibitors, and all the evidence of record indicates that they inhibit granzyme activity directly. See Bird, discussed above, and pages 4, 6, 7 and 15 of the specification. Appellants have not identified any evidence which would indicate that serpins have any effect on transcription or translation of nucleic acids encoding granzymes, or even the degradation or destabilization of granzymes. Thus, it appears that the serpin and serpin mimetic sub-genus does not include members that inhibit granzyme transcription or translation, etc. We find that the amendment narrowing claim 34 to serpins or serpin mimetics did not go far enough, and had the unfortunate effect of creating a sub-genus that was never described in the specification – in other words, it had the effect of introducing new matter into the claim. This same problem arises in claim 64.

Summary

We reverse the enablement rejection of claims 26-35, 37-40, 42-44, 48-50 and 61-74 under 35 U.S.C. § 112, first paragraph, and vacate the written description rejection of claims 26-35, 37, 42-44, 48-50, 61-65, 67 and 71-73 under 35 U.S.C. § 112, first paragraph. In addition, we enter a new ground of rejection against claims 34 and 64 under the provisions of 37 CFR § 41.50(b).

Time Period for Response

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 CFR § 41.50(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .
>
> (2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

REVERSED-IN-PART; VACATED-IN-PART; 37 CFR § 41.50(b)

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